The Special approval for Spikevax during public health emergency or pandemic situation by the Brunei Darussalam Medicines Control Authority (BDMCA) is for use and supply as directed by the Government of Brunei Darussalam.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Spikevax bivalent Original / Omicron 0.1 mg/mL dispersion for injection
elasomeran / imelasomeran
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial that contains 5 doses of 0.5 mL each.

One dose (0.5 mL) contains 25 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles) and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

Elasomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Imelasomeran is a single-stranded mRNA, 5'-capped, encoding a full-length, codon-optimised pre-fusion stabilised conformation variant (K983P and V984P) of the SARSCoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
White to off white dispersion (pH: 7.0 – 8.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spikevax bivalent Original / Omicron is indicated as a booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Booster dose
Individuals 18 years of age and older

A booster dose of Spikevax bivalent Original / Omicron (0.5 mL, containing 50 micrograms mRNA) should be given intramuscularly to individuals 18 years of age and older at least 3 months after completion of a primary series or booster with a COVID-19 mRNA vaccine or adenoviral vector vaccine.

Paediatric population
The safety and efficacy of Spikevax bivalent Original / Omicron in adolescents and children less than 18 years of age have not yet been established. No data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥65 years of age.

Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported in individuals who have received Spikevax (original). Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. Subsequent doses of the vaccine should not be given to those who have experienced severe allergic reactions (e.g. anaphylaxis, generalised urticaria) to an earlier dose of Spikevax (original) or Spikevax bivalent Original / Omicron.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax (original) or Spikevax bivalent Original / Omicron.

These cases have primarily occurred within 14 days following vaccination, more often after the second dose, and more often in younger men.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.

Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose (100 micrograms) of Spikevax (original) or a booster dose (50 micrograms) of Spikevax (original) or Spikevax bivalent Original / Omicron has not yet been characterised.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Spikevax bivalent Original / Omicron may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with all vaccines, vaccination with Spikevax bivalent Original / Omicron may not protect all vaccine recipients.

Excipients with known effect

Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL dose, that is to say, essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Spikevax (original) or Spikevax bivalent Original / Omicron with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Spikevax in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of Spikevax in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Spikevax is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Spikevax bivalent Original / Omicron has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Participants 18 years of age and older
The safety of Spikevax (original) was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of Spikevax (original) (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Adolescents 12 through 17 years of age
Safety data for Spikevax (original) in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 3,726 participants 12 through 17 years of age who received at least one dose of Spikevax (n=2 486) or placebo (n=1,240) (NCT04649151). Demographic characteristics were similar among participants who received Spikevax (original) and those who received placebo.

The most frequent adverse reactions in adolescents 12 to 17 years of age were injection site pain (97%), headache (78%), fatigue (75%), myalgia (54%), chills (49%), axillary swelling/tenderness

(35%), arthralgia (35%), nausea/vomiting (29%), injection site swelling (28%), injection site erythema (26%), and fever (14%).

Children 6 through 11 years of age
Safety data for Spikevax (original) in children were collected in an ongoing Phase 2/3 two-part randomised, observer-blind clinical study conducted in the United States and Canada (NCT04796896). Part 1 is an open-label phase of the study for safety, dose selection, and immunogenicity and included 380 participants 6 through 11 years of age who received at least 1 dose (0.25 mL) of Spikevax (original). Part 2 is the placebo-controlled phase for safety and included 4,016 participants 6 through 11 years of age who received at least one dose (0.25 mL) of Spikevax (original) (n=3,012) or placebo (n=1,004). No participants in Part 1 participated in Part 2. Demographic characteristics were similar among participants who received Spikevax (original) and those who received placebo.

The most frequent adverse reactions in participants 6 through 11 years of age following administration of the primary series were injection site pain (98.4%), fatigue (73.1%), headache (62.1%), myalgia (35.3%), chills (34.6%), nausea/vomiting (29.3%), axillary swelling/tenderness (27.0%), fever (25.7%), injection site erythema (24.0%), injection site swelling (22.3%), and arthralgia (21.3%).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in children and individuals 6 years of age and older

The safety profile presented below is based on data generated in several placebo-controlled clinical studies of Spikevax (original):
- 30,351 adults ≥ 18 years of age
- 3,726 adolescents 12 through 17 years of age
- 4,002 children 6 years through 11 years of age
- and post-marketing experience.

Adverse reactions reported are listed according to the following frequency convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (Table 1).

Table 1: Adverse reactions from Spikevax (original) clinical trials and post-authorisation experience in children and individuals 6 years of age and older

MedDRA System Organ Class	Frequency	Adverse reaction(s)
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
	Rare	Acute peripheral facial paralysis** Hypoaesthesia Paraesthesia
Cardiac disorders	Very rare	Myocarditis Pericarditis

Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling Injection site erythema
	Common	Injection site urticaria Injection site rash Delayed injection site reaction***
	Uncommon	Injection site pruritus
	Rare	Facial swelling****

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases.
**Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the Spikevax group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
***Median time to onset was 9 days after the first injection, and 11 days after the second injection. Median duration was 4 days after the first injection, and 4 days after the second injection.
****There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination

The reactogenicity and safety profile in 343 subjects receiving Spikevax (original), that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Spikevax (original) booster dose – participants 18 years of age and older
The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax (original) are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax (original) vaccine primary series. In an open-label phase of this study, 167 of those participants received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose of the primary series. The solicited adverse reaction profile for the booster dose (0.25 mL, 50 micrograms) was similar to that after the second dose in the primary series.

Spikevax bivalent Original / Omicron booster dose – participants 18 years of age and older
The safety, reactogenicity, and immunogenicity of a second booster dose of Spikevax bivalent Original / Omicron are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the Spikevax bivalent Original / Omicron 50 microgram booster dose, and 377 participants received the Spikevax (original) 50 microgram booster dose.

Spikevax bivalent Original / Omicron had a reactogenicity profile similar to that of Spikevax (original) given as a second booster dose. The frequency of adverse reactions after immunisation with Spikevax bivalent Original / Omicron was also similar to that of a first booster dose of Spikevax (original) (50 micrograms) and relative to the second dose of the Spikevax (original) primary series (100 micrograms). No new safety signals were identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system through the Adverse Event Following Immunisation (AEFI) Reporting Form available from the National Adverse Drug Reaction Monitoring Centre (NADRMC) and the nearest government pharmacy facility (hospital/health centre) and include batch/Lot number if available. The completed AEFI Reporting Form should be returned to the nearest government pharmacy facility (hospital/health centre) or e-mailed at nadrmc.dps@moh.gov.bn.

4.9 Overdose

No case of overdose has been reported.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

Elasomeran and imelasomeran contains RNA encapsulated in lipid nanoparticles.

The RNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the RNA into cells for translation into viral protein. The delivered RNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19.

Clinical efficacy of Spikevax (original) in adults

The adult study was a randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) that excluded individuals who were immunocompromised or had received immunosuppressants within 6 months, as well as participants who were pregnant, or with a known history of SARS-CoV-2 infection. Participants with stable HIV disease were not excluded. Influenza vaccines could be administered 14 days before or 14 days after any dose of Spikevax (original). Participants were also required to observe a minimum interval of 3 months after receipt of blood/plasma products or immunoglobulins prior to the study in order to receive either placebo or Spikevax (original).

A total of 30,351 subjects were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 subjects who received either Spikevax (original) (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS. 98% of vaccine recipients received the second dose 25 days to 35 days after dose 1 (corresponding to -3 to +7 days around the interval of 28 days).

COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy overall and by key age groups are presented in Table 2.

Table 2: Vaccine Efficacy Analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – Per-Protocol Set

Age Group (Years)	Spikevax			Placebo			
	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	% Vaccine Efficacy (95% CI)*
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)**
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

[#]COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*Vaccine efficacy and 95% confidence interval (CI) from the stratified Cox proportional hazard model
** CI not adjusted for multiplicity. Multiplicity adjusted statistical analyses were carried out in an interim analysis based on less COVID-19 cases, not reported here.

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

The vaccine efficacy of Spikevax (original) to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% confidence interval 88.6, 96.5%).

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Clinical efficacy of Spikevax (original) in adolescents 12 through 17 years of age

The adolescent study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study (NCT04649151) to evaluate the safety, reactogenicity, and efficacy of Spikevax (original) in adolescents 12 to 17 years of age. Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732 participants were randomised 2:1 to receive 2 doses of Spikevax (original) or saline placebo 1 month apart.

A secondary efficacy analysis was performed in 3,181 participants who received 2 doses of either Spikevax (original) (n=2,139) or placebo (n=1,042) and had a negative baseline SARS-CoV-2 status in the Per Protocol Set. Between participants who received Spikevax (original) and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose.

There were zero symptomatic COVID-19 cases in the Spikevax (original) group and 4 symptomatic COVID-19 cases in the placebo group.

Immunogenicity of Spikevax (original) in adolescents 12 through 17 years of age

A non-inferiority analysis evaluating SARS-CoV-2 50% neutralising titres and seroresponse rates 28 days after Dose 2 was conducted in the Per-Protocol immunogenicity subsets of adolescents aged 12 through 17 (n=340) in the adolescent study and in participants aged 18 through 25 (n=296) in the adult study. Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The geometric mean ratio (GMR) of the neutralising antibody titres in adolescents 12 to 17 years of age compared to the 18- to 25-year-olds was 1.08 (95% CI: 0.94, 1.24). The difference in seroresponse rate was 0.2% (95% CI: -1.8, 2.4). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Clinical efficacy of Spikevax (original) in children 6 through 11 years of age

The paediatric study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical study to evaluate the safety, reactogenicity, and effectiveness of Spikevax (original) in children aged 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomised 3:1 to receive 2 doses of Spikevax (original) or saline placebo 1 month apart.

A secondary efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of 10 November 2021 was performed in 3,497 participants who received two doses (0.25 mL at 0 and 1 month) of either Spikevax (original) (n=2,644) or placebo (n=853) and had a negative baseline SARS-CoV-2 status in the Per Protocol Set. Between participants who received Spikevax (original) and those who received placebo, there were no notable differences in demographics.

COVID-19 was defined as symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose.

There were three COVID-19 cases (0.1%) in the Spikevax (original) group and four COVID-19 cases (0.5%) in the placebo group.

Immunogenicity of Spikevax (original) in children 6 through 11 years of age

An analysis evaluating SARS-CoV-2 50% neutralising titres and seroresponse rates 28 days after Dose 2 was conducted in a subset of children aged 6 through 11 years (n=319) in the paediatric study and in participants aged 18 through 25 years (n=295) in the adult study. Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralising antibody titres in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.239 (95% CI: 1.072, 1.432). The difference in seroresponse rate was 0.1% (95% CI: -1.9, 2.1). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Immunogenicity in participants 18 years of age and older – after Spikevax (original) booster dose (0.25 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax (original) are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax (original) vaccine as primary series. In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose in the primary series. A

single booster dose (0.25 mL, 50 micrograms) was shown to result in a geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29) in neutralising antibodies from pre-booster compared to 28 days after the booster dose. The GMFR in neutralising antibodies was 1.53 (95% CI: 1.32, 1.77) when compared 28 days post dose 2 (primary series) to 28 days after the booster dose.

Immunogenicity in participants 18 years of age and older – after Spikevax bivalent Original / Omicron booster dose (0.5 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax bivalent Original / Omicron are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). Study P205 Part G and Part F enrolled participants who had previously received 2 doses of Spikevax (original) (100 micrograms) as a primary series and a booster dose of Spikevax (original) (50 micrograms) at least 3 months prior to enrollment. In Part G, 437 participants received a second booster dose of Spikevax bivalent Original / Omicron (50 micrograms). In Part F, 377 participants received a second booster dose of Spikevax (original) (50 micrograms). The Part F group serves as a within-study, non-contemporaneous comparator group to the Spikevax bivalent Original / Omicron group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set that includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster) (Table 3).

Table 3. Ancestral SARS-CoV-2 (D614G) and Omicron (BA.1) neutralising antibody titres (ID_{50}) - Spikevax bivalent Original / Omicron 50 µg and Spikevax (original) 50 µg administered as second booster doses

	Omicron variant		**Ancestral SARS-CoV-2**	
Antibody: PsVNA nAb ID_{50} titres	**P205 Part G Spikevax bivalent Original / Omicron 50 µg (N=334)**	**P205 Part F Spikevax (original) 50 µg (N=260)**	**P205 Part G Spikevax bivalent Original / Omicron 50 µg (N=334)**	**P205 Part F Spikevax (original) 50 µg (N=260)**
Pre-booster, n	334	260	334	260
Observed GMT (95% CI)[a]	298.1	332.0	1266.7	1521.0
	(258.8, 343.5)	(282.0, 390.9)	(1120.2, 1432.5)	(1352.8, 1710.2)
Day 29, n	334	260	334	260
Observed GMT (95% CI)[a]	2372.4	1473.5	5977.3	5649.3
	(2070.6, 2718.2)	(1270.8, 1708.4)	(5321.9, 6713.3)	(5056.8, 6311.2)
Observed GMFR (95% CI)[a]	8.0	4.4	4.7	3.7
	(7.2, 8.8)	(4.0, 5.0)	(4.4, 5.1)	(3.4, 4.0)
GLSM [estimated GMT] (95% CI)[b]	2479.9	1421.2	6422.3	5286.6
	(2264.5, 2715.8)	(1283.0, 1574.4)	(5990.1, 6885.7)	(4887.1, 5718.9)
GMR (97.5% CI)[b]	**1.7 (1.5, 2.0)**		**1.2 (1.1, 1.4)**	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold-rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome-2; n = number of participants with non-missing data at the corresponding timepoint.

[a] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

[b] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titres, and age groups.

Observed neutralising antibody titres for Omicron subvariants BA.4/5 after Spikevax bivalent Original / Omicron booster dose

Table 4 presents the summary of the observed neutralising antibody GMTs and GMFRs against Omicron BA.4/BA.5 for participants who received either the Spikevax bivalent Original /Omicron 50 microgram booster vaccine (Part G) or the Spikevax (original) 50 microgram booster vaccine (Part F)

as a second booster dose (4th dose). This exploratory analysis was conducted in the immunogenicity set that includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster).

Table 4. Summary of neutralising antibody geometric mean titres for the Omicron BA.4/BA.5 variant - comparison between Spikevax bivalent Original / Omicron 50 µg and Spikevax (original) 50 µg booster doses

	PPSI - Neg	
	P205 Part G Spikevax bivalent Original / Omicron 50 µg (N=334)	**P205 Part F Spikevax (original) 50 µg (N=260)**
Pre-booster, n[a]	334	260
Observed GMT (95% CI)[a,b]	115.6	139.7
	(98.5, 135.6)	(119.5, 163.3)
Day 29, n[a]	333	260
Observed GMT (95% CI)[a,b]	727.4	492.1
	(632.8, 836.1)	(431.1, 561.9)
Observed GMFR (95% CI)[a,b]	6.3	3.5
	(5.7, 6.9)	(3.2, 3.9)
GLSM [Estimated GMT] (95% CI)[b]	776.4 (719.5, 837.9)	458.3 (420.6, 499.3)
GMR (95% CI)[b]	**1.7 (1.5, 1.9)**	

Abbreviations: CI = confidence interval; GLSM=geometric least squares mean; GMFR = geometric mean fold-rise (post-baseline/baseline titres); GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LOD = limit of detection; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PPSI = per-protocol set for immunogenicity; PPSI – Neg = per-protocol Set for immunogenicity – SARs-CoV-2 Negative at baseline; PPSI – Pos = per-protocol Set for immunogenicity – SARS-CoV-2 Positive at baseline; PsVNA = pseudotyped virus neutralization assay.

Note: antibody values reported as below the lower limit of detection are replaced by 0.5 x LOD.

[a] Number of subjects with non-missing data at the timepoint (baseline or post-baseline).

[b] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

Immunogenicity of a booster dose of Spikevax (original) following primary vaccination with another authorised COVID-19 vaccine in adults 18 years of age and older

Safety and immunogenicity of a heterologous booster with Spikevax (original) were studied in an investigator-initiated study with 154 participants. The minimum time interval between primary series using a vector-based or RNA-based COVID-19 vaccine and booster injection with Spikevax (original) was 12 weeks (range: 12 weeks to 20.9 weeks). The dose used for boosting in this study was 100 micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were assessed on Day 1 prior to administration and at Day 15 and Day 29 after the booster dose. A booster response was demonstrated regardless of primary vaccination.

Only short-term immunogenicity data are available; long-term protection and immunological memory are currently unknown.

Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) in the UK

COV-BOOST is a multicentre, randomised Phase 2 investigator-initiated study of third dose booster vaccination against COVID-19 with a subgroup to investigate detailed immunology. Participants were adults aged 30 years or older, in good physical health (mild to moderate well-controlled co-morbidities were permitted), who had received two doses of either Pfizer–BioNTech or Oxford–AstraZeneca (first dose in December 2020, January 2021 or February 2021), and were at least 84 days post second dose by the time of enrolment. Spikevax (original) boosted antibody and neutralising responses and was well tolerated regardless of the prime series. The dose used for boosting in this study was 100

micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were assessed on Day 28 after the booster dose.

Spikevax (original) - pre-boost and post-boost neutralising antibody against the B.1.617.2 (Delta) variant in adults

Results of the pseudovirus neutralisation assay (PsVNA) against the B.1.617.2 (Delta) variant determined pre-booster and on Day 29 post-booster showed that administration of a booster dose of Spikevax (original) (0.25 mL, 50 micrograms) in adults induced a 17-fold rise in neutralising antibodies against the Delta variant compared with pre-booster levels (GMFR = 17.28; 95% CI: 14.38, 20.77; n=295).

Spikevax (original) - neutralising antibody against the B.1.617.2 (Delta) variant in children 6 through 11 years of age

Serum samples of the per-protocol immunogenicity subset (n=134) of the ongoing paediatric study obtained at baseline and on Day 57 were tested in a PsVNA based on the B.1.617.2 (Delta) variant. In children 6 through 11 years of age, the GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant (measured by PsVNA). Furthermore, 99.3% of children met the definition of seroresponse.

Elderly
Spikevax (original) was assessed in individuals 6 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of Spikevax (original) was consistent between elderly (≥65 years) and younger adult subjects (18-64 years). Spikevax bivalent Original / Omicron was assessed in 437 individuals 18 years of age and older (P205 Part G, safety analysis set), including 38 subjects 75 years of age and older. A total of 174 of the 437 participants (39.8%) were ≥ 65 years of age.

Paediatric population
The licensing authority has deferred the obligation to submit the results of studies with Spikevax (original) and Spikevax bivalent Original / Omicron in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low.

Genotoxicity/carcinogenicity

In vitro and *in vivo* genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low. Carcinogenicity studies were not performed.

Reproductive toxicity

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of Spikevax was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of Spikevax vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate)
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG)
Trometamol
Trometamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened multidose vial (0.1 mg/mL)

9 months at -50ºC to -15ºC.

After removal from the freezer, the unopened vaccine vial may be stored refrigerated at 2°C to 8°C, protected from light, for a maximum of 30 days. Within this period, up to 12 hours may be used for transportation at 2°C to 8°C (see section 6.4).

Once thawed, the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 24 hours after removal from refrigerated conditions.

Punctured multidose vial (0.1 mg/mL)
Chemical and physical in-use stability has been demonstrated for 19 hours at 2°C to 25ºC after initial puncture (within the allowed use period of 30 days at 2°C to 8ºC and including 24 hours at 8°C to 25ºC). From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Multidose vial (0.1 mg/mL)

Store frozen between -50ºC to -15ºC.
Keep the vial in the outer carton to protect from light.
For storage conditions after thawing and first opening, see section 6.3.

Transportation of thawed multidose vials (0.1 mg/mL) in liquid state at 2°C to 8°C
If transport at -50°C to -15°C is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2°C to 8°C (within the 30 days shelf life at 2°C to 8°C). Once thawed and transported in liquid state at 2°C to 8°C, vials should not be refrozen and should be stored at 2°C to 8°C until use.

6.5 Nature and contents of container

Multidose vial (0.1 mg/mL)

2.5 mL dispersion in a (type 1 glass or type 1 equivalent glass or cyclic olefin polymer with inner barrier coating) multidose vial with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal).

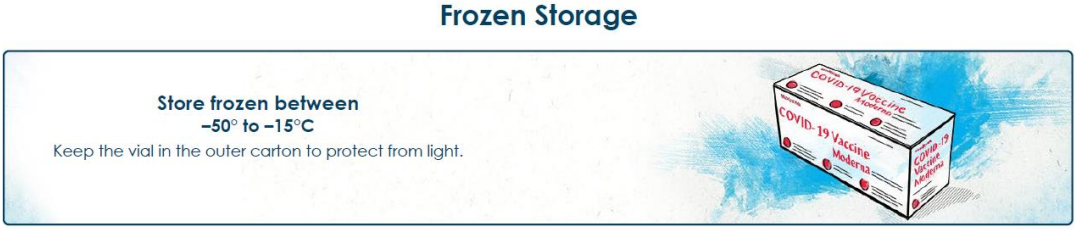
Each vial contains 2.5 mL.

Pack size: 10 multidose vials

6.6 Special precautions for disposal and other handling

The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the dispersion.

Thawed vials and filled syringes can be handled in room light conditions.



Multidose vial (0.1 mg/mL)

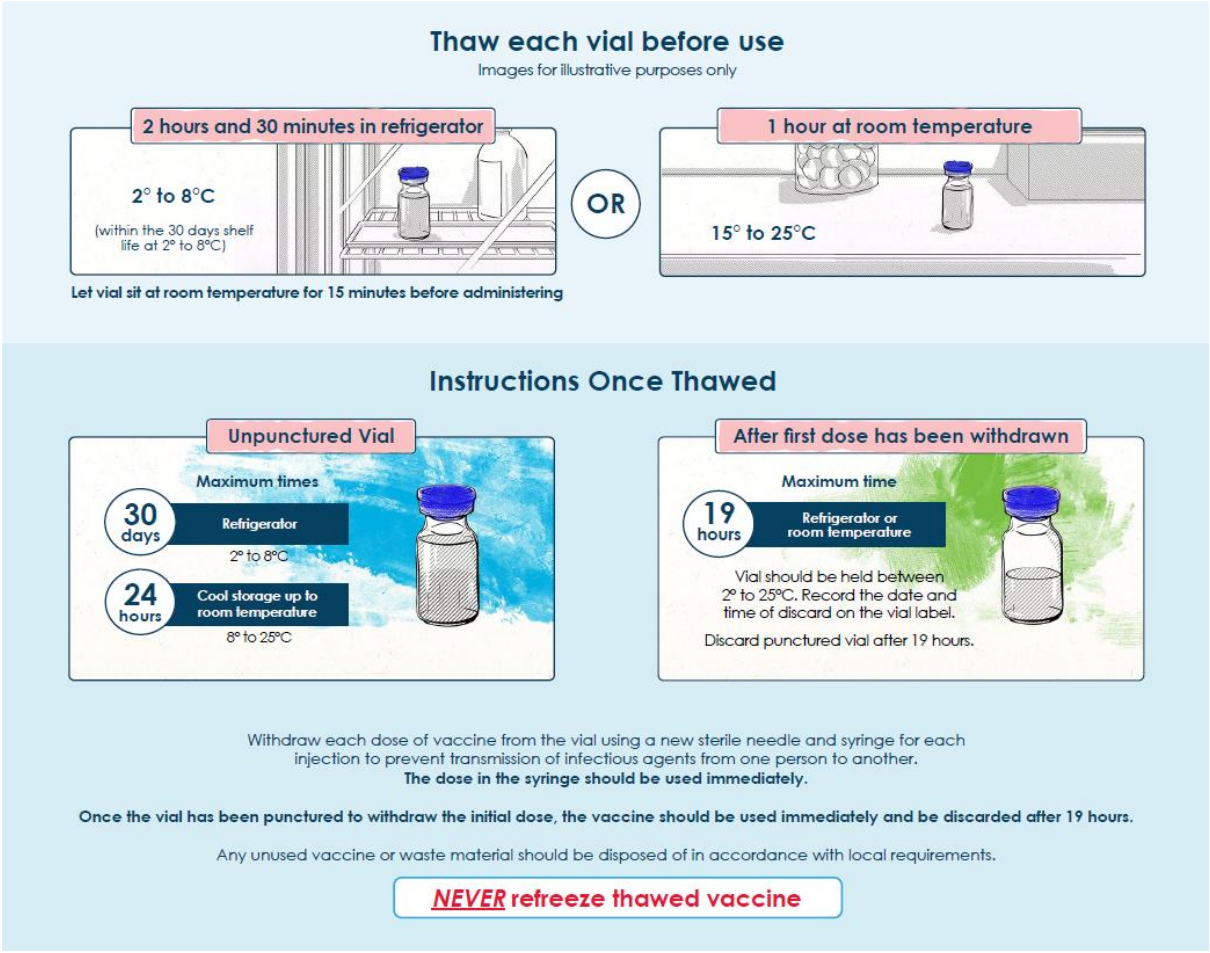
The vaccine comes ready to use once thawed.

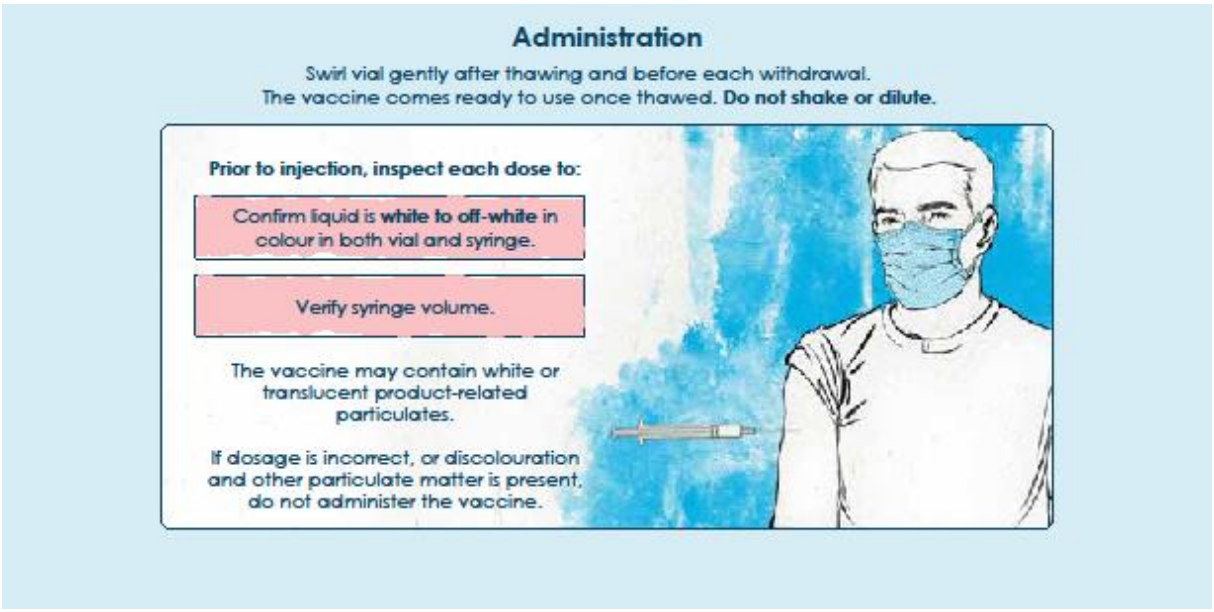
Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

Five (5) doses (of 0.5 mL each) can be withdrawn from each vial (blue flip-off cap).

Pierce the stopper preferably at a different site each time.

An additional overfill is included in each vial to ensure that 5 doses of 0.5 mL can be delivered.





7. PRODUCT OWNER

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8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 April 2021

9. DATE OF REVISION OF THE TEXT

26 September 2022